



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>C07N 1/00, A61K 31/715</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 92/22585</b> <b>(43) International Publication Date:</b> 23 December 1992 (23.12.92)
<b>(21) International Application Number:</b> PCT/US92/04594 <b>(22) International Filing Date:</b> 5 June 1992 (05.06.92) <b>(30) Priority data:</b> 712,880 11 June 1991 (11.06.91) US 799,751 27 November 1991 (27.11.91) US  <b>(71) Applicant:</b> PATENT BIOPHARMACEUTICS, INC. [US/ US]; 2856 West 33rd Street, Erie, PA 16506 (US). <b>(72) Inventor:</b> GALLINA, Damian, J. ; 2856 West 33rd Street, Erie, PA 16506 (US). <b>(74) Agents:</b> WHITE, Paul, E., Jr. et al.; Cushman, Darby & Cushman, Ninth Floor, 1100 New York Avenue, N.W., Washington, DC 20005-3918 (US).		<b>(81) Designated States:</b> AT (European patent), AU, BE (Euro- pean patent), CA, CH (European patent), DE (Euro- pean patent), DK (European patent), ES (European pa- tent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), NO, SE (European patent).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> METHODS OF TREATING HEMORRHOIDS AND ANORECTAL DISEASE  <b>(57) Abstract</b>  A method of treating hemorrhoids and anorectal disease which includes applying to the hemorrhoids and anorectal tissues an effective amount of a composition including a pharmaceutically acceptable carrier and hyaluronic acid or pharmaceutically acceptable salts thereof.		

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METHODS OF TREATING HEMORRHOIDS AND  
ANORECTAL DISEASE

BACKGROUND OF THE INVENTION

5       The present invention relates to methods  
of treating hemorrhoids and diseases of the  
anorectum employing novel pharmaceutical  
compositions. In particular, the present invention  
relates to topical applications of hyaluronate  
preparations as rectal bonding and adhesion agents,  
10   anti-inflammatory agents and bio-repair materials.  
The use of hyaluronate preparations employs their  
properties to reduce the inflammation, pain,  
swelling, and sequelae of injured, irritated,  
diseased, strained, or traumatized anorectal tissues  
15   while adhering to and protecting sensitive tissues  
of the anorectum. The source of the hyaluronate  
used in the treatment compositions may be a  
hyaluronic acid or any acceptable salt form of  
hyaluronic acid. The term "hyaluronate" is often  
20   used to mean "hyaluronic acid equivalent" which  
equates to hyaluronic acid of varying molecular  
weights and any of their salt forms.

      Hyaluronic acid is a naturally occurring  
mucopolysaccharide with a molecular weight generally  
25   ranging between about 50,000 and 8,000,000 (or  
possibly higher), depending on the sources of the  
hyaluronate and the analytical methods used in its  
determination.

      Methods of obtaining highly-pure or ultra-  
30   pure hyaluronic acid and its salt forms, isolation  
techniques, and analytical methods for testing  
purity are provided, for example, in the U.S.

patents, numbered 3,396,081, 4,141,973, 4,517,295,  
4,736,024, 4,784,990 and 4,808,576.

Hyaluronic acid is well known, being found  
in the joint tissue and vitreous humor of the eyes  
5 of mammals. It has been extracted from rooster  
combs, human umbilical cords and bacterial cultures  
such as those of hemolytic group A and C  
streptococci for various therapeutic purposes. One  
of the first therapeutic uses of this material was  
10 as a replacement for the liquid vitreous of the  
human eye to aid in ophthalmic surgery, especially  
in the treatment of retinal detachment. It has also  
been used for the relief of trauma or irritation in  
joint tissue of mammals including humans by  
15 injection into the synovial fluid of the joint.

An extensive discussion of its various  
uses is found in U.S. Patent No. 4,141,973. The  
administration of hyaluronic acid alone and with  
cortisone in various animal joints, especially  
20 horses, is discussed in the article by Rydell et  
al., "Effect of Intra-articular Injection of  
Hyaluronic Acid on the Clinical Symptoms of  
Osteoarthritis and on Granulation Tissue Formation",  
Clinical Orthopaedics and Related Research, October,  
25 1971, No. 80. The use of hyaluronic acid in human  
joints is reported in the "Preliminary Clinical  
Assessment of Na Hyaluronate Injection into Human  
Arthritic Joints" by Peyron et al., Pathologic  
Biologic, October, 1974, Vol. 22, No. 8. The use of  
30 hyaluronic acid in reducing fibrotic wound reactions  
is reported in the article by Rydell, "Decreased  
Granulation Tissue Reaction After Installment of  
Hyaluronic Acid", Acta Orthop. Scandinav, Vol. 41.

Hyaluronic acid and derivatives thereof can play a critical role in wound healing.

Hyaluronate preparations are already marketed by several companies as products utilized in eye surgery, hip repair, dentistry, cosmetics, skin treatments, and dermatology.

U.S. Patent No. 4,736,024 describes the use of hyaluronic acid or a molecular weight fraction thereof as a vehicle for pharmacologically active substances. The vehicle may be in suppository form for transcutaneous absorption to obtain a systemic effect. In contrast, the present methods of treatment employ the bonding, protective, healing, therapeutic, and curative properties of hyaluronic acid and derivatives thereof for their direct, local therapeutic affect when applied topically to thrombosed anorectal vessels, inflamed tissues of the anorectum, rectal fissures, and/or pruritis ani. In the present invention, hyaluronic acid (and its derivatives) is the active pharmaceutical agent.

For the present invention, pharmaceutical preparations containing less than 0.1% to more than 25.0% hyaluronate have been made and applied topically to the anorectum in successfully relieving the tenderness, soreness, pain, burn, itch, and discomfort of inflamed, irritated anorectal tissues. Hyaluronate reduces pain, inflammation, and swelling due to its anti-inflammatory and membrane stabilizing properties. Hyaluronate protects sensitive tissues and vessels of the anorectal epithelium and rectal mucosa by adhering to them and can remarkably mask the trauma of inflamed tissues.

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SUMMARY OF THE INVENTION

The present invention relates to a method of treating hemorrhoids and other anorectal diseases by topically applying to hemorrhoidal and anorectal tissues a pharmaceutical preparation comprising a hyaluronate acid moiety such as hyaluronic acid or an acceptable salt form of hyaluronic acid, in an effective amount for the treatment of anorectal disease. The disease states of the anorectum include but are not limited to hemorrhoids, rectal fissures, inflamed anorectal tissues, pruritis ani and proctitis.

It is accordingly one important object of the present invention to provide a method for promoting the healing of traumatized, injured, irritated, inflamed, or diseased anorectal tissues while reducing the pain, burn, inflammation, itch, and swelling of these tissues by means of the topical application of a hyaluronate preparation. The hyaluronate preparation displays a powerful anti-inflammatory action on anorectal tissues.

An important advantage of using hyaluronate for anorectal treatment is that while sodium hyaluronate, for example, may be compared to hydrocortisone in its anti-inflammatory affect, unlike hydrocortisone or other glucocorticoids, sodium hyaluronate is not catabolic in nature. Hyaluronic acid and its derivatives stabilize cellular membranes, reduce inflammation and enhance the anabolic process as opposed to the catabolic process.

It is a related object of the present invention to provide an improved method of treating hemorrhoids and other anorectal problems by utilizing the advantageous bonding and adhering properties as well as the anti-inflammatory and healing properties of hyaluronic acid and its various salt forms.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

10 Pain, discomfort, tenderness, inflammation, and swelling are reduced when hyaluronic acid or an acceptable salt form of hyaluronic acid are applied directly to irritated, inflamed, traumatized, strained, or injured tissues  
15 of the anorectum. One embodiment of the present invention is the use of hyaluronate in the treatment of hemorrhoidal and other anorectal disease conditions employing the anti-inflammatory property of hyaluronic acid and its derivatives.

20 Another embodiment of the present invention is to employ the property of hyaluronic acid and its derivatives to bond or strongly adhere to tissues of the anorectum in methods of treatment, which provides a protective coating on irritated,  
25 inflamed, sore, tender, and sensitive anorectal tissues, such as hemorrhoids.

A further embodiment of the present invention is to employ the property of hyaluronic acid and its derivatives to promote the healing of  
30 injured, irritated, strained, diseased or traumatized anorectal tissues.

Additional embodiments of the present invention include: (1) treatment of internal and external hemorrhoids; (2) treatment of inflamed anorectal tissues; (3) treatment of rectal fissures; 5 (4) treatment of pruritis ani; and (5) treatment of proctitis.

Any pharmaceutically acceptable form of hyaluronic acid may be used in the present invention. This application will for the most part, 10 however, be principally concerned with the representative use of the readily available commercial forms of hyaluronate, such as hyaluronic acid, the potassium salt of hyaluronic acid, and more preferably sodium hyaluronate. This in no way 15 limits the forms of hyaluronic acid employed in the present invention

Hyaluronic acid and derivatives thereof may be incorporated into numerous types of gels, creams, ointments, lotions, pastes, salves, liquids, 20 and/or solid suppository vehicles. Sterile distilled water alone and simple cream, ointment and suppository bases may be employed as carriers of the hyaluronic acid and derivatives. Examples of suppository bases and suspending vehicles include 25 Fattibase<sub>™</sub> (polyethylene glycol base), Vehicle-S<sub>™</sub> (acrylic polymer resin base), and Polybase<sub>™</sub> (polyethylene glycol base) by Paddock Laboratories, Inc., Minneapolis, Minnesota. Such pharmaceutically acceptable carriers are readily available for 30 preparing the present formulations and have desirable pH's, melting points, and preservatives.

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In its more specific aspects, the preferred concentration of hyaluronate in the treatment formulation ranges from about 0.01% to 25.0% by weight and more preferably from about 0.1% to 20.0% by weight and most preferably from about 1.0% to 10.0% by weight.

Additional therapeutic agents may be added to the present formulations as medically indicated, selected from the classes of: keratolytics, surfactants, counter-irritants, humectants, antiseptics, lubricants, astringents, wound healing agents, emollients, additional adhesion/coating protectants, additional anti-inflammatory agents, vasoconstrictors, anticholinergics, corticosteroids (e.g. glucocorticoids) and anesthetics. Preservatives and buffers may also be added.

The invention is further illustrated by the following examples:

#### EXAMPLES

##### Exemplary Hyaluronate Preparations of the Present Invention

The present hyaluronate preparations may be formulated as a solid, gel, paste, cream, salve, lotion, liquid, ointment, and powder, depending on the ingredients and the amounts used.

Example A) Twelve (12) suppositories were prepared containing 0.5% sodium hyaluronate assuming the average weight of the suppository to be 2.0 gm and allowing for a 10% overfill and shrinkage:

5

1. Melt 26.268 gm of Polybase<sub>TM</sub>, a preblended suppository base consisting of a homogenous mixture of various molecular weight polyethylene glycols with a specific gravity of 1.777 at 25°C, in a pyrex beaker over a hot plate or water bath;

10

2. add 0.132 gm of finely powdered sodium hyaluronate to the heated Polybase<sub>TM</sub> with continuous agitation;
3. pour into suppository mold and chill; and
4. trim excess with razor blade or spatula.

15

Calculations: 26.268 gm Polybase<sub>TM</sub>  
+ 0.132 gm Sodium Hyaluronate  
= 26.400 gm Total Blend

One suppository = 2.0 gm

Each suppository contains 0.5%

20

(10 mg) sodium hyaluronate.

A total of 12 suppositories were prepared.

25

Example B) Twelve (12) suppositories were prepared containing 1% sodium hyaluronate and 1% hydrocortisone, following the procedure described in Example A:

1. melt 25.872 gm Polybase<sub>TM</sub>;

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2. add 0.264 gm Sodium Hyaluronate;
3. add 0.264 gm Hydrocortisone; and
4. repeat steps 3 and 4 of Example A.

5

Calculations: 25.872 gm Polybase<sub>TM</sub>  
+ 0.264 gm Sodium Hyaluronate  
+ 0.264 gm Hydrocortisone  
= 26.400 gm Total blend

10

One suppository = 2.0 gm  
Each suppository contains 1% (20mg)  
of sodium hyaluronate and 1%  
(20mg) of hydrocortisone.  
A total of 12 suppositories were prepared.

15

Example C) A 100 gm sample of a 2 1/2% sodium  
hyaluronate cream based formulation was  
prepared containing the following components:

20

12.0 gm Sterile H<sub>2</sub>O  
5.5 gm Propylene glycol  
15.0 gm Polyethylene glycol-400  
2.5 gm Sodium Hyaluronate  
6.0 gm Vehicle-S<sub>TM</sub>, a preblended aqueous  
vehicle containing carboxypolymethylene,  
polysorbate 80, simethicone and  
methylparaben, 0.18% as a preservative.  
9.0 gm Polyethylene glycol-8000 (melt)  
30.0 gm Polybase<sub>TM</sub> (melt)  
20.0 gm Fattibase<sub>TM</sub> (melt), a preblended base  
consisting of a homogenous mixture of  
triglycerides from coconut, palm and palm  
kernel oils.

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100.0 gm Total

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Example D) A 2% sodium hyaluronate cream based formulation containing 1% hydrocortisone and 1% pramoxine HCL was prepared containing the following components:

5	14.0 gm Sterile H <sub>2</sub> O
	6.0 gm Propylene glycol
	13.0 gm Polyethylene glycol-400
	2.0 gm Sodium Hyaluronate
	1.0 gm Hydrocortisone
10	1.0 gm Pramoxine HCL
	7.0 gm Vehicle-S <sub>11</sub>
	9.0 gm polyethylene glycol-8000
	27.0 gm Polybase <sub>11</sub>
	27.0 gm Fattibase <sub>11</sub>
15	<hr/>
	100.0 gm Total

Example E) A 7% hyaluronate cream based formulation containing 5% Lidocaine HCL was prepared containing the following components:

20	15.0 gm Sterile H <sub>2</sub> O
	5.0 gm Propylene glycol
	10.0 gm Polyethylene glycol-400
	7.0 gm Sodium Hyaluronate
	5.0 gm Lidocaine HCL
25	6.0 gm Vehicle-S <sub>11</sub>
	8.0 gm Polyethylene glycol-8000
	24.0 gm Polybase <sub>11</sub>
	20.0 gm Fattibase <sub>11</sub>
30	<hr/>
	100.0 gm Total

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Example F) A 5% hyaluronate ointment containing 2% benzocaine was prepared containing the following components:

10 gm Sterile H<sub>2</sub>O  
7 gm Propylene glycol  
15 gm Polyethylene glycol-400  
5 gm Sodium Hyaluronate  
2 gm Benzocaine  
8 gm Vehicle-S<sub>11</sub>  
10 gm Polyethylene glycol-8000  
10 gm Polybase<sub>11</sub>  
22 gm Fattibase<sub>11</sub>  
11 gm Aquaphor, a preblended cholesterolized anhydrous water miscible ointment base consisting of petrolatum, mineral oil, mineral wax, and woolwax alcohol.

100 gm Total

Example G) Stable gel formulations of hyaluronate were prepared using only water as the vehicle, containing the components as respectively listed:

1. 2.5% formulation = 2.5 gm Sodium Hyaluronate  
+ 97.5 gm Sterile H<sub>2</sub>O (QS)  
Total 100.0 gm of a 2.5% gel formulation.

2. 5.0% formulation = 5.0 gm Sodium Hyaluronate  
+ 95.0 gm Sterile Water (QS)  
Total 100.0 gm of a 5% gel formulation.

Numerous formulations may be derived by varying the concentrations of the above mentioned ingredients of the above Examples and may be determined by the desired characteristics of the finished products. It should also be remembered that other vehicle systems are available for this purpose and therefore this disclosure is not limited to the examples given.

First Exemplary Clinical Evaluation

The efficaciousness of the present methods of treating anorectal disease states was demonstrated by the following clinical evaluation:

- a. Eighty individuals suffering from external and internal hemorrhoids and rectal fissures were selected for the study.
- b. The patients were randomly divided into two groups: a control group and the test group.
- c. The control group (40 patients) was subjected to standard medical treatment for external thrombosed hemorrhoids. This treatment entailed use of conventional sitz-baths, limited physical activity and conventional controlled diet (e.g. high fiber, low fat). The test group (40 patients) was subjected to the same treatment but also treated with a topical cream containing a specific concentration of sodium hyaluronate as the active ingredient. The three different concentrations of sodium hyaluronate used in this study were: 2.0%, 3.5% and 5.0%.
- d. The hyaluronate preparations were topically applied 2-4 times daily via fingercoats by each member of the test group.

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- 5 e. After the initial consultation by the patients with the physician, a nurse contacted each patient by phone every day for one week for the purpose of monitoring each patient. Each patient visited and consulted with the rectal and colon surgeon-physician once a week for a total of five visits. One patient-physician visit/week multiplied by 5 weeks multiplied by 80 patients = 400 patient-physician visits.
- 10 f. The following parameters were determined and statistically compared: (1) Pain-free time intervals; (2) reduction of swelling (resolving of thrombosed conditions; and (3) general improvement of the anorectum. Hypothesis testing was performed at the 5% significance level.
- 15 (i) 65.0% of the experimental group (26 patients) experienced pain free time intervals of 4 hours or longer following rectal application of a sodium hyaluronate preparation.
- 20 (ii) 20% of the control group (8 patients) reported pain free time intervals of one hour or longer following sitz bath treatment.
- (iii) No member of the control group reported pain free time intervals greater than 2 hours following standard treatment methods only.
- 25 (iv) 80% of the control group (32 patients) experienced pain free time intervals of one hour or less following sitz bath treatment only.

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- (v) The experimental group reported less painful bowel movements when a sodium hyaluronate preparation was applied to the anorectal canal within one hour prior to defecation. There were no reported improvements in defecating in the control group following the standard treatment modalities.

- g. This study conclusively proves the utility and benefit of using the present hyaluronate preparations in the methods of the present invention for treatment of anorectal disease conditions by relieving pain and enhancing healing of injured or diseased anorectal tissues.

#### Second Exemplary Clinical Evaluation

The efficaciousness of the present methods of treating anorectal disease states was again demonstrated by the following second clinical evaluation:

- a. A 2% sodium hyaluronate cream based formulation was prepared containing the following components:

20	2% Sodium hyaluronate
	1% Benzyl alcohol
	1.5% Sodium propionate
	2.25% Fattibase™
	0.75% Lecithin
25	0.75% Glycerin
	0.75% Polyethylene glycol - 4000
	91% Sterile H <sub>2</sub> O
	<hr/>
	100%

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b. Twenty patients suffering from anorectal disorders were selected for the study. The disorders and number of patients having the disorders were as follows:

- 5           8 patients had either perianal irritation or pruritis ani;  
          4 patients had grade 1-2 bleeding hemorrhoids;  
          4 patients had fissures (two chronic with  
10           sphincter spasm, one superficial and one with a large AIDS (Acquired Immune Deficiency Syndrome) ulceration);  
          3 patients had prolapsing hemorrhoids; and  
          1 patient had a thrombosed external hemorrhoid.

15           c. The 20 patients were supplied with 20 gram tubes containing the above 2% sodium hyaluronate preparation. Pile pipe rectal applicators were provided with the tubes for those patients requiring such applicators. The patients were instructed to  
20           topically apply the hyaluronate preparation three times each day, either digitally or by applicator as appropriate. The study period was two weeks.

          d. The patients were initially observed by a physician. The patients were instructed to complete a  
25           questionnaire at the end of the two-week study period to determine whether the hyaluronate preparation was effective. The following parameters were determined for each patient:

- 30           1) the effectiveness of the hyaluronate preparation after application, being rated as effective either a) every time, b) sometime or c) not at all; and

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2) the overall effectiveness of the hyaluronate preparation, being rated as a) excellent, b) good, c) fair or d) poor.

5 e. The results of the study showed that 18 of the 20 patients (90%) rated the hyaluronate preparation to be effective either every time (6 patients) or sometime (12 patients). These patients who rated the cream as effective in turn rated the preparation as  
10 excellent (6 patients), good (9 patients), and fair (3 patients). Thus, 75% of the patients rated the hyaluronate preparation as good or excellent.

- (i) The hyaluronate preparation relieved symptoms of itching, burning, bleeding, irritation and pain, depending upon the anorectal disorder.
- 15 (ii) The two patients who rated the cream as ineffective had anorectal disorders resulting from mechanical type problems.
- (iii) Significantly, the patient with the AIDS ulceration, which is typically a difficult  
20 problem to treat, found great relief by employing the hyaluronate preparation.

f. This study conclusively proves the utility and benefit of using the present hyaluronate preparations and the methods of the present invention for  
25 treatment of anorectal disease conditions by relieving pain and enhancing healing of injured or diseased anorectal tissues.

While only a few exemplary embodiments of this invention have been described in detail, those skilled

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in the art will recognize that there are many possible variations and modifications which may be made in the exemplary embodiments while yet retaining many of the novel and advantageous features of this invention.

5 Accordingly, it is intended that the following claims cover all such modifications and variations.

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CLAIMS:

1. A method of treating hemorrhoids and anorectal disease which comprises applying to the hemorrhoids and anorectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or pharmaceutically acceptable salts thereof.
2. The method of claim 1 wherein said composition includes hyaluronic acid or a pharmaceutically suitable salt thereof in an amount of 0.01 to 25.0% by weight.
3. The method of claim 1 wherein said composition includes hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount of 0.1-20.0% by weight.
4. The method of claim 1 wherein said composition includes hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount of 1.0-10.0% by weight.
5. The method of claim 1 wherein said composition further includes an additive selected from the group consisting of keratolytics, surfactants, counter-irritants, humectants, antiseptics, lubricants, astringents, emollients, wound healing agents, adhesion/coating protectants, vasoconstrictors, anticholinergics, corticosteroids, anesthetics and anti-inflammatory agents.
6. The method of claim 1 wherein said composition is in a form selected from the group consisting of gel, solid, paste, salve, lotion, liquid, cream, ointment and powder.

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7. The method of claim 1 wherein said carrier is water.

8. A method of treating inflammation of anorectal tissues which comprises applying to anorectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically suitable salt thereof.

9. A method of treatment for providing a protective coating on hemorrhoids and anorectal diseased tissues which comprises applying an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof.

10. A method of treatment by promoting healing of hemorrhoids and anorectal disease which comprises applying to hemorrhoids and anorectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof.

11. A method of treating rectal fissures which comprises applying to rectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof.

12. A method of treating pruritis ani which comprises applying to anorectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof.

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13. A method of treating proctitis which comprises applying to anorectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a  
5 pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/04594

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07N 1/00; A61K 31/715

US CL :536/55.3, 54, 18.7; 514/54,825

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/55.3, 54, 18.7; 514/54,825

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS (hemorrhoids, anorectal diseases, hyalurenic acid, anti-inflammatory agents, surfactants, corticosteroids, wound healing agents) Dialog ( see search terms above)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,736,024 (Della Valle et al) 05 April 1988, ENTIRE DOCUMENT.	1-13
Y	US, A, 3,594,473 (Hunger et al) 20 July 1971, ENTIRE DOCUMENT.	1-13
Y	US, A, 4,808,576 (Schultz et al) 28 February 1989, ENTIRE DOCUMENT.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

27 JULY 1992

Date of mailing of the international search report

20 AUG 1992

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